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Uveitis: treatment guidelines

Uveítes: diretrizes terapêuticas

Uveítis: guías de tratamiento

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ABSTRACT

The objective of this study was to establish evidence-based guidelines for the treatment of uveitis. The Brazilian Council of Ophthalmology, in partnership with the Brazilian Medical Association and the Brazilian Society of Uveitis, has created guidelines to standardize the procedures for the treatment of uveitis. We searched the Medline and Pubmed databases dated until August 2015 to find indications of intravitreal injections/implants and the use of immunosuppressants for the treatment of uveitis.

Keywords:
Uveitis.
Immunosuppressive Agents.
Adrenal Cortex Hormones.
Ttherapeutic Use.

RESUMO

Esta publicação tem como objetivo estabelecer diretrizes baseadas em evidências científicas para tratamento da uveíte. A necessidade de normatização de condutas em uveítes foi a principal motivação para o Conselho Brasileiro de Oftalmologia, em parceria com a Associação Médica Brasileira e Sociedade Brasileira de Uveíte, promover a elaboração das diretrizes. Foi realizada busca de evidência na base de informação científica Medline / Pubmed até agosto de 2015 para abordar as indicações de injeções / implantes intravítreos e uso de imunossupressores em uveítes.

Palavras-Chave:
Uveíte.
Imunossupressores.
Corticosteroides.
Uso Terapêutico.

RESUMEN

Esta publicación tiene como objetivo establecer las directrices basadas en la evidencia científica para el tratamiento de la uveítis. La necesidad de una regulación de las tuberías en la uveítis fue la motivación principal para el Consejo Brasileño de Oftalmología, en colaboración con la Asociación Médica Brasileña y la Sociedad Brasileña de uveítis, promoviendo el desarrollo de las directrices. Búsqueda de pruebas se llevó a cabo en la base de información científica Medline / Pubmed hasta agosto de 2015 para hacer frente a los signos de inyecciones intravítreas / implantes y el uso de la terapia inmunosupresora en uveítis.

Palabras Clave:
Uveítis.
Inmunosupresores.
Corticoesteroides.
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INTRODUCTION

Uveitis cases account for 2%–3% of ophthalmologic visits in emergency units; this limited presentation indicates that most ophthalmologists are not familiar with this condition.[1,2]

The Brazilian Council of Ophthalmology, in partnership with the Brazilian Medical Association and the Brazilian Society of Uveitis, has created guidelines to standardize the procedures for the treatment of uveitis.

Medical guidelines are implementable standards that assist in decision-making in clinical and surgical cases. These guidelines help standardize the safety of evidence-based procedures and professional ethics.

However, it is critical to emphasize that physician autonomy should be preserved.

METHODS

These guidelines were created after the analysis of relevant clinical complications associated with the treatment of uveitis. We searched for scientific information in the Medline and Pubmed databases dated until August 2015.

GUIDELINES

Our analysis indicated that oral and topical corticosteroids are the basis of treatment for most uveitis cases; however, prolonged use of oral corticosteroids causes undesirable and potentially severe side effects, which limits their use and warrants the adoption of alternative therapies. Prednisone doses ranging from 5.0 to 7.5 mg/day are considered physiological doses because they are compatible with the natural daily production of cortisol in the body. Other treatment strategies should be considered in patients requiring larger doses for prolonged periods in order to avoid adverse events, such as hypertension, diabetes mellitus, osteoporosis, hepatic steatosis, and pancreatitis. In addition, patients with these clinical conditions should avoid the prolonged use of oral corticosteroids.[3,4] Therapeutic options for uveitis include intravitreal injections/implants and immunosuppressants.

1. DETAILS ON THE INTRAVITREAL INJECTION/IMPLANT OF CORTICOSTEROIDS:

1.1 They are a therapeutic option for the treatment of noninfectious unilateral posterior/intermediate uveitis for patients in whom treatment with systemic corticosteroids caused adverse events or in patients with contraindications to the prolonged use of systemic corticosteroids;[5]

1.2 They are a treatment option for patients with uveitis controlled with >10 mg/day prednisone for a prolonged period to avoid complications associated with the use of systemic corticosteroids;[5]

1.3 Injection of dexamethasone has been described as an adjuvant therapy in infectious cases provided that it is associated with intravitreal antibiotic therapy; examples include patients with toxoplasmic retinochoroiditis and patients who are either intolerant to or not eligible for the proposed treatment;[6,7,8]

1.4 They are used as an adjunctive therapy in endophthalmitis;[9,10,11]

1.5 Terapia adjuvante na endoftalmite.[12,13]

The two forms of administration of intravitreal corticosteroids are injection and slow-release implant. Table 1 summarizes the main features of intravitreal corticosteroids.[5,14,15,16,17,18]

Table 1. General characteristics of intravitreal corticosteroids

Drug	Presentation Duration of effect	Considerations
Triamcinolone acetate	40 mg/ml 3 months	Shorter duration of the effect on aphakic or vitrectomized eyes
Dexamethasone	0.4 mg/0.1 ml 72 h	Shorter duration of the effect, which minimizes adverse events but limits the therapeutic effect and consequently drug use; may be adjuvant in the treatment of infectious uveitis
Slow-release implant of dexamethasone (Ozurdex®)	0.7 mg Peak at 2 months and steady course for 6 months	High cost

Slow-release implant of fluocinolone acetonide	0.59 mg and 2.1 mg 30 months	Increased intraocular pressure compared with other drugs Not available in Brazil

The complications due to intravitreal corticosteroids include ocular hypertension, cataract, retinal detachment, vitreous hemorrhage, endophthalmitis, crystalline lesion, and reactivation of infectious retinitis.[5,19]

Intraocular pressure (IOP) can be monitored 30 min after drug injection and at subsequent intervals that depend on the drug.

- After the use of triamcinolone: Assess IOP 1 week after treatment, every 2 weeks for the first month, and then monthly for up to 6 months.
- After the use of dexamethasone implant: Assess IOP 2 weeks after treatment, every 2 weeks in the first month, and then monthly for up to 6 months.
- After the use of fluocinolone acetonide implant: Assess IOP after 2 weeks of therapy, every 2 weeks in the first month, and then monthly up to 9 months.[19]

2. INTRAVITREAL INJECTION OF ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR (ANTI-VEGF) AGENTS

Anti-VEGF agents, such as ranibizumab (Lucentis®), bevacizumab (Avastin®), and aflibercept (Eylea®), are used in some uveitis cases but are considered off-label, meaning that its indication is not described in the prescription leaflet. Therefore, the patient should be informed about this and the physician should take responsibility for procedures involving these medications.

Some studies have reported the use of anti-VEGFs in patients with uveitis as a treatment option for macular edema that is unresponsive to corticosteroids and subretinal neovascular membranes. The use of anti-VEGFs has also been used for ischemic occlusive vasculitis, which stimulates the release of VEGFs; this complication occurs in patients with tuberculosis, Behçet's disease, sarcoidosis, and systemic lupus erythematosus, the latter of which is associated with photocoagulation.[5,20,21,22,23,24,25,26,27]

The advantages of anti-VEGFs compared with corticosteroids are the lower probability of complications, such as cataracts, increased intraocular pressure, retinal detachment, vitreous hemorrhage, and endophthalmitis.[5]

3. INTRAVITREAL INJECTION OF BIOLOGICAL AGENTS

Few studies have evaluated the intravitreal use of infliximab in patients with noninfectious uveitis, and the results are controversial. This lack of consistent scientific evidence limits the indication of this drug.[5,28,29,30,31]

4. USE OF IMMUNOSUPPRESSANTS[3,4,32]

Immunosuppressants are indicated for patients who have used high prednisone doses for more than 1 month or for those in whom there is absence of satisfactory control after 2–4 weeks of prednisone use.

They are also indicated for patients whose inflammatory status is controlled with high prednisone doses and for the suspension or reduction of prednisone to doses <10 mg/day after the management of uveitis. These cases include the following:

- Systemic diseases are chronic and may involve other organs and therefore may be treated with immunosuppressants to avoid complications associated with the prolonged use of prednisone at doses >10 mg/day. These diseases include Behçet's disease, Vogt–Koyanagi–Harada syndrome, sympathetic ophthalmia, severe cases of sarcoidosis, uveitis associated with seronegative spondyloarthropathies, and juvenile idiopathic arthritis.
- Sclerites, especially when associated with systemic diseases such as granulomatosis with polyangeitis
- Severe presentations of white dot syndromes such as serpiginous choroiditis and birdshot chorioretinopathy

The choice of immunosuppressant depends on the patient's clinical condition and on any comorbidities or underlying diseases. Multidisciplinary follow-up with a rheumatologist or general practitioner is recommended to adequately monitor the patient's condition when uveitis is associated with chronic disease and to check for side effects. The corticosteroid dose should be gradually reduced 4–8 weeks after the introduction of the immunosuppressant.Os imunossupressores mais utilizados são metotrexato, azatioprina, ciclosporina, micofenolato mofetil, ciclosfosfamida e agentes biológicos (infliximabe e adalimumabe). O quadro 2 resume as principais características dos imunossupressores.

Table 2. General characteristics of immunosuppressants

Immunosuppressant	Dose Onset of the effect	Follow-up	Complications	Considerations
Methotrexate	7.5–25.0 mg 1x week 2–12 weeks	Every 1–2 months: Blood count Hepatogram	Gastrointestinal intolerance Fatigue Hepatotoxicity Interstitial pneumonia Alopecia Rash Myelosuppression	Antimetabolite Dihydrofolate reductase inhibitor Orally IM or SC reduce side effects
Azathioprine	1–3 mg/kg/day orally 4–12 weeks	Every 4–6 weeks: Blood count Hepatogram	Gastrointestinal intolerance Hepatotoxicity Myelosuppression	Purine antimetabolite Caution in users of allopurinol
Cyclosporine	2–5 mg/kg/day 2x day orally 2–6 weeks	Measurement of BP Creatinine: Biweekly until dose stabilization and then monthly	Nephrotoxicity Hypertension Hepatotoxicity Hirsutism Hyperuricemia Myalgia Paresthesia Gingival hyperplasia	Inhibitor of calcineurin and T-cell proliferation Fluid intake is recommended
Cyclophosphamide	1–3 mg/kg/day orally 2–8 weeks	Blood count and ESA weekly up to dose stabilization and then monthly	Myelosuppression Hemorrhagic cystitis Ovarian failure Azoospermia Alopecia Nausea/vomiting	Alkylating agent Recommend fluid intake
Mycophenolate Mofetil	1g 2x day orally 2–12 weeks	Blood count weekly up to 4 weeks, biweekly for 2 months, and then monthly 3 months: Hepatogram	Gastrointestinal intolerance Leukopenia Fatigue Myalgia Headache	Antimetabolite Inosine monophosphate dehydrogenase inhibitor Caution in cases of renal failure and gastrointestinal disorders that impair drug absorption
Infliximab (Remicade®)	3 mg/kg/day every 4–8 weeks* intravenously 1–8 weeks	Blood count Hepatogram Variable frequency	Infections Lymphoma Hypersensitivity Skin reactions	Anti-TNFα Perform a purified protein derivative tuberculin skin test (PPD-TST)to discard latent TB before starting treatment Contraindicated in cases of congestive heart failure
Adalimumab (Humira®)	40 mg/0.8 mL every 1–2 weeks* SC			Anti-TNFα Perform PPD-TST to discard latent TB before starting treatment

IM: intramuscular; SC: subcutaneous; BP: blood pressure; ESA: trace element and sediment abnormalities

* The dose and interval between doses may vary according to the underlying disease and age.

Promising biological agents for the treatment of noninfectious uveitis are rituximab (B-lymphocyte inhibitor), gevokizumab (monoclonal antibody that binds to IL-1β), and tocilizumab (anti-IL6 monoclonal antibody).[32,33,34]

CONCLUSIONS

Individualized treatment is critical for adequate control of uveitis, and no single therapy resolves all cases of the disease. A risk–benefit assessment should be performed for each therapeutic option. The choice of treatment depends on disease presentation, cause, and the patient's clinical condition. Although oral corticosteroids are widely used, chronic cases requiring long-term use or adverse events may prevent the continuation of this therapy, and the alternatives presented in this study should be considered. Although intravitreal treatments are advantageous because they prevent systemic adverse events, the use of immunosuppressants is indicated in bilateral cases and cases associated with systemic diseases. However, new biological agents should be used with caution; although their indication is well established in systemic autoimmune diseases, few studies to date have evaluated these drugs in the treatment of uveitis. Testing of uveitis treatments is limited by the rarity of the disease as research requires multicenter studies and recruitment of patients with noninfectious uveitis of different etiologies that may present distinct responses to treatment. Particular attention should be given to infectious etiologies that require associated antimicrobial coverage.

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